

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/005389

International filing date (day/month/year)
21.12.2004

Priority date (day/month/year)
23.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07C231/12, C07C233/23, C07C409/40

Applicant
ANGIOGENE PHARMACEUTICALS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/GB2004/005389

AP20 Rec'd PCT/PTO 23 JUN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20,22-29
	No: Claims	21
Inventive step (IS)	Yes: Claims	1-19,22-29
	No: Claims	20,21
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	

2. Citations and explanations**see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

PCT/GB2004/005389

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1: WO-A-9902166

D2: WO-A-0040259

NOVELTY (Article 33(2) PCT)**CLAIMS 1-19 & 22 (YES)**

The processes of Claims 1-19 and 22 are novel, since no prior art discloses the preparation of ZD6126 phenol from the corresponding benzylic derivative, D1 (cf. page 8, line 21 to page 9, line 17) describing a process wherein colchicine (and derivatives thereof) is hydrolysed and subjected to ring contraction with alkaline hydrogen peroxide.

CLAIM 20 (YES)

The subject-matter of Claim 20 is novel, since the two ZD6126 alcohols disclosed in D2 (cf. Exs. 24 & 25) are excluded by way of proviso.

CLAIM 21 (NO)

The subject-matter of Claim 21 is not new, since D2 (cf. Exs. 24 & 25) describes processes for the preparation of a ZD6126 alcohol of formula (II) as defined in present Claim 6 wherein R² are both Me (cf. Ex. 24) or H (cf. Ex. 25) by the reaction of allocolchicine with methyllithium in ether/THF and with LiAlH₄ in ether/THF respectively.

CLAIMS 23-29 (YES)

The subject-matter of Claims 23-29 is novel, since no prior art discloses the ZD6126-alkene, -hydroperoxide and -dimer of formulae (III), (IV) or (V) respectively, such that the intermediates of formulae (III), (IV) or (V) *per se* (cf. Claims 23, 26 & 29), methods for their preparation (cf. Claims 24 & 27), and their use in the preparation of ZD6126 phenol (cf. Claims 25 & 28), are novel.

INVENTIVE STEP (Article 33(3) PCT)**CLAIMS 1-19 & 22 (YES)**

In the light of D1 (cf. page 8, line 21 to page 9, line 17), which describes a process for the preparation of ZD6126 phenol by hydrolysis of colchicine (and derivatives thereof), followed by ring contraction with alkaline hydrogen peroxide, the problem to be solved by the present invention may be regarded as the provision of an alternative

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process for the preparation of ZD6126 phenol.

The solution provided by the process of Claim 1, namely by reacting a ZD6126 alcohol of formula (II) with an acid catalyst and an oxidising agent is considered to be inventive, since none of the cited prior art suggests preparing ZD6126 phenol by such a benzylic alcohol to phenol transformation. Thus the processes of Claims 1-5, and Claims 6-19 (including the additional step of preparing a ZD6126 alcohol from an allocolchicine), and the use of a ZD6126 alcohol for preparing ZD6126 phenol (cf. Claim 22) are all inventive.

CLAIMS 20-21 (NO)

The subject-matter of Claims 20 and 21 does not involve an inventive step. Thus as stated above, D2 (cf. Exs. 24 & 25) describes processes for the preparation of a ZD6126 alcohol of formula (II) as defined in present Claims 1 or 6 wherein R^2 are both Me (cf. Ex. 24) or H (cf. Ex. 25) by the reaction of allocolchicine with methyllithium in ether/THF, and with $LiAlH_4$ in ether/THF respectively. D2 further teaches compounds represented by formula (I) therein wherein R^1 - R^3 are methyl, R^4 and R^6 are H, X is $CHNHCOCH_3$ as in Exs. 24 & 25, and wherein R^5 may be C_{1-7} alkyl substituted by one or more of OH and phenyl i.e. a formula which overlaps substantially with the present formula (II) of Claim 20, it being clear from D2 that these compounds may be prepared by processes analogous to those of Exs. 24 & 25 i.e. according to the process of present Claim 21.

CLAIMS 23-29 (YES)

The compounds of formulae (III), (IV) and (V) are all compounds which may be formed as intermediates in the reaction of ZD6126 alcohol to ZD6126 phenol and thus these compounds *per se* (cf. Claims 23, 26 & 29), methods for their preparation (cf. Claims 24 & 27), and their use in the preparation of ZD6126 phenol (cf. Claims 25 & 28), are all inventive.

OTHER COMMENTS

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.